HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRIFTIN safely and effectively. See full prescribing information for PRIFTIN.

PRIFTIN (rifapentine) tablet, film coated for oral use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

- Rifapentine is a rifamycin antimycobacterial indicated for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis* in combination with one or more antituberculosis drugs. (1)

DOSAGE AND ADMINISTRATION

- PRIFTIN has been studied for the treatment of tuberculosis caused by drug-susceptible organisms as part of regimens consisting of an initial 2 month phase followed by a 4 month continuation phase. (2.1)
- PRIFTIN should not be used alone in either the initial or the continuation phases of antituberculous treatment. (2.1)
- **Initial Phase (2 Months):** 600 mg twice weekly for two months by direct observation of therapy, with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other antituberculosis drugs. (2.1)
- **Continuation Phase (4 Months):** 600 mg once weekly for 4 months by direct observation therapy with isoniazid or another appropriate antituberculous agent. (2.1)
- Concomitant administration of pyridoxine (Vitamin B6) is recommended in order to avoid INH-associated peripheral neuropathy. (2.2)
- Take with food. (2.2)

DOSAGE FORMS AND STRENGTHS

- 150 mg tablets. (3)

CONTRAINDICATIONS

Known hypersensitivity to any rifamycin. (4.1)

WARNINGS AND PRECAUTIONS

- Do not use as a once weekly Continuation Phase regimen with isoniazid in HIV seropositive patients due to the risk of failure and/or relapse with rifampin-resistant organisms. (5.1, 14)
- Co-administration with Protease Inhibitors and Reverse Transcriptase Inhibitors. (5.2, 7.1)
- Higher relapse rates occur in patients with cavitary pulmonary lesions and/or positive sputum cultures after the initial phase of treatment or those with evidence of bilateral pulmonary disease: Use cautiously. (5.3)
- Hepatotoxicity: In patients with abnormal liver tests/disease monitor liver tests prior to therapy and every 2–4 weeks during therapy. If signs of disease occur or worsen, discontinue therapy. (5.4)
- Hyperbilirubinemia: Repeat testing and reassess patient. (5.5)
- Discoloration of body fluids: May permanently stain contact lenses or dentures red-orange. (5.6)
- Porphyria: Avoid use in these patients. (5.7)
- *Clostridium difficile*-associated colitis: Evaluate if diarrhea occurs. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are hyperuricemia, pyuria, hematuria, urinary tract infection, proteinuria, lymphopenia, neutropenia, anemia, and hypoglycemia. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Protease Inhibitors and Reverse Transcriptase Inhibitors. (5.2, 7.1)
- Hormonal Contraceptives: Use another means of birth control. (7.2)
- May increase metabolism and decrease the activity of drugs metabolized by cytochrome P450 3A4 and 2C8/9. Dosage adjustments may be necessary if given concomitantly. (7.3)

USE IN SPECIFIC POPULATIONS

- Pediatrics: The safety and effectiveness under the age of 12 has not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PRIFTIN® is indicated for the treatment of pulmonary tuberculosis caused by *Mycobacterium tuberculosis*. PRIFTIN must always be used in combination with one or more antituberculosis drugs to which the isolate is susceptible depending on the phase of treatment *[see Dosage and Administration (2) and Clinical Studies (14)]*.

Limitations of Use

PRIFTIN should not be used as a once weekly Continuation Phase regimen in combination with isoniazid in HIV seropositive patients with pulmonary tuberculosis because of a higher rate of failure and/or relapse documented with the presence of rifampin-resistant organisms *[see Warnings and Precautions (5.1)* and *Clinical Studies (14)]*.

PRIFTIN has not been studied as part of the Initial Phase treatment regimen in HIV seropositive patients with pulmonary tuberculosis.

PRIFTIN should not be used as monotherapy in either the initial or the continuation phases of antituberculous treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

PRIFTIN has been studied for the treatment of tuberculosis caused by drug-susceptible organisms as part of regimens consisting of an initial 2 month phase followed by a 4 month continuation phase.

These recommendations apply only to the treatment of patients with drug-susceptible organisms.

Initial Phase (2 Months) of short course treatment for pulmonary tuberculosis:

PRIFTIN should be administered at a dose of 600 mg (4 × 150 mg tablets) twice weekly for two months by direct observation of therapy**,** with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other antituberculosis drugs as part of an appropriate regimen which includes daily companion drugs such as ethambutol, pyrazinamide, and streptomycin.

The determination of the companion drugs to be used should be made by the treating physician and depends on the results of susceptibility testing as well as the phase of treatment. PRIFTIN has been studied as part of the initial regimen with isoniazid, pyrazinamide and ethambutol *[see Clinical Studies (14)]*.

Continuation Phase (4 Months) of short course treatment for pulmonary tuberculosis:

Following the Initial Phase (2 months), Continuation Phase (4 months) treatment may consist of PRIFTIN 600 mg once weekly for 4 months in combination with isoniazid or an appropriate antituberculosis agent for susceptible organisms by direct observation therapy.

PRIFTIN was studied as a component of a 4 month continuation phase in conjunction with INH 900 mg once a week in two clinical studies *[see Clinical Studies (14)]*.

The prescribing physician is directed to current guidelines for further direction on other possible components of the Continuation Phase regimen as well as for directions on extending this phase.

2.2 Administration

Take PRIFTIN with meals. Administration of rifapentine with a meal increases oral bioavailability and may reduce the incidence of gastrointestinal upset, nausea, and/or vomiting. *[see Clinical Pharmacology (12.3)]*.

In patients with conditions which predispose them to neuropathy (e.g., nutritional deficiency, HIV infection, renal failure, alcoholism, as well as pregnant and breastfeeding women), concomitant administration of pyridoxine (Vitamin B6) is recommended in order to avoid INH-associated peripheral neuropathy (see American Thoracic Society/Centers for Disease Control/Infectious Disease Society of America Guideline for the Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children).

3 DOSAGE FORMS AND STRENGTHS

PRIFTIN is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed "Priftin" on top and "150" on the bottom.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

PRIFTIN is contraindicated in patients with a history of hypersensitivity to rifamycins.

5 WARNINGS AND PRECAUTIONS

5.1 HIV Seropositive Patients

PRIFTIN should not be used as a once weekly Continuation Phase regimen in combination with isoniazid in HIV seropositive patients with pulmonary tuberculosis because of a higher rate of failure and/or relapse documented with the presence of rifampin-resistant organisms *[see Clinical Studies (14)]*.

PRIFTIN has not been studied as part of the Initial Phase treatment regimen in HIV seropositive patients with pulmonary tuberculosis.

5.2 Protease Inhibitors and Reverse Transcriptase Inhibitors

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of PRIFTIN with other drugs metabolized by these enzymes, such as protease inhibitors and reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor. *[see Drug Interactions (7.1 and 7.2)* and *Clinical Pharmacology (12.3)]*

5.3 Relapse of Tuberculosis

PRIFTIN should be used cautiously in subjects with cavitary pulmonary lesions and/or positive sputum cultures after the initial phase of treatment or in those with evidence of bilateral pulmonary disease due to higher rates of relapse. *[see Clinical Studies (14)]*.

Poor compliance with the dosage regimen, particularly during the initial phase in the companion antituberculosis drugs administered with rifapentine, is associated with late sputum conversion and a high relapse rate. Therefore, compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed *[see Patient Counseling Information (17)]*.

Higher relapse rates have also been seen in HIV positive patients receiving PRIFTIN during the continuation phase. Risk factors for relapse included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and age (younger) *[see Clinical Studies (14)]*.

5.4 Hepatotoxicity

Since antituberculous multidrug treatments, including the rifamycin class, are associated with serious hepatic events, patients with abnormal liver tests and/or liver disease should only be given rifapentine in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver tests (especially serum transaminases) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of liver disease occur or worsen, rifapentine should be discontinued. Hepatotoxicity of other antituberculosis drugs (eg, isoniazid, pyrazinamide) used in combination with rifapentine should also be taken into account.

5.5 Hyperbilirubinemia

Hyperbilirubinemia resulting from competition for excretory pathways between rifapentine and bilirubin cannot be excluded since competition between the related drug rifampin and bilirubin can occur. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

5.6 Discoloration of Body Fluids
PRIFTIN may produce a predominately red-orange discoloration of body tissues and/or fluids (eg, skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid).
Contact lenses or dentures may become permanently stained.

5.7 Porphyria
PRIFTIN should not be used in patients with porphyria. Rifampin has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration. Based on these isolated reports with rifampin, it may be assumed that rifapentine has a similar effect.

5.8 *Clostridium difficile*-Associated Diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including the rifamycins, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions
The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:
- Hypersensitivity *[see Contraindications (4.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Hyperbilirubinemia *[see Warnings and Precautions (5.5)]*
- Discoloration of Body Fluids *[see Warnings and Precautions (5.6)]*
- Porphyria *[see Warnings and Precautions (5.7)]*
- *Clostridium difficile*-Associated Diarrhea *[see Warnings and Precautions (5.8)]*

6.2 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The data described below reflect exposure to PRIFTIN in a randomized, open label, active-controlled trial of patients with pulmonary tuberculosis, excluding those with HIV-infection. The population consisted of primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2 month phase of treatment (60 days), 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin in combination with isoniazid, pyrazinamide and ethambutol all administered daily. Ethambutol was discontinued when drug susceptibly testing was completed. During the 4 month continuation phase, 321 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid and 307 patients in the rifampin arm received twice weekly rifampin and isoniazid. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period.
Twenty-two deaths occurred in the study (eleven in the rifampin combination therapy group and eleven in the rifapentine combination therapy group).
In the study, 18/361 (5.0%) rifampin combination therapy patients discontinued the study due to an adverse reaction compared to 11/361 (3.0%) rifapentine combination therapy patients. Three patients (two rifampin combination therapy patients and one rifapentine combination therapy patient) were discontinued in the Initial Phase as a result of hepatitis with increased liver function tests (ALT, AST, LDH, and bilirubin). Concomitant medications for all three patients included isoniazid, pyrazinamide, ethambutol, and pyridoxine. The two rifampin patients and one rifapentine patient recovered without sequelae.
As shown in Table 1, hyperuricemia was the most frequently reported reaction and was most likely related to the pyrazinamide since only two cases were reported in the Continuation Phase when this drug was no longer included in the treatment regimen.
Seven patients had adverse reactions associated with an overdose. In the rifampin combination group these reactions included hematuria, anorexia, back pain, arthralgia, and myalgia. In the rifapentine combination group these reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

The following table (Table 1) presents treatment-emergent adverse reactions associated with the use of any of the four drugs in the regimens (rifapentine/rifampin, isoniazid, pyrazinamide, or ethambutol) which occurred in ≥1% of patients during treatment and post-treatment through the first three months of follow-up.

Table 1. Treatment-Emergent Adverse Reactions Occurring in ≥1% of Patients

	Initial Phase*		***Continuation Phase**†*		***Total**‡*	
System Organ Class Preferred Term	***Rifapentine Combination (N=361) N(%)***	***Rifampin Combination (N=361) N(%)***	***Rifapentine Combination (N=304) N(%)***	***Rifampin Combination (N=317) N(%)***	***Rifapentine Combination (N=361) N(%)***	***Rifampin Combination (N=361) N(%)***
RENAL & URINARY						
Pyuria	39 (10.8)_	56 (15.5)	47 (14.8)	36 (11.8)	78 (21.6)	83 (23.0)
Proteinuria	36 (10.0)	53 (14.7)	14 (4.4)	27 (8.9)	47 (13.0)	71 (19.7)
Hematuria	39 (10.8)	38 (10.5)	32 (10.1)	27 (8.9)	64 (17.7)	61 (16.9)
Urinary Tract Infection	32 (8.9)	24 (6.6)	23 (7.3)	10 (3.3)	48 (13.3)	32 (8.9)
Urinary Casts	20 (5.5)	22 (6.1)	11 (3.5)	7 (2.3)	29 (8.0)	28 (7.8)
Cystitis	5 (1.4)	6 (1.7)	1 (0.3)	1 (0.3)	6 (1.7)	7 (1.9)
METABOLIC & NUTRITIONAL						
Hyperuricemia	115 (31.9)	83 (23.0)	0 (0.0)	2 (0.7)	115 (31.9)	83 (23.0)
Hyperkalemia	14 (3.9)	22 (6.1)	20 (6.3)	21 (6.9)	33 (9.1)	41 (11.4)
Hypoglycemia	22 (6.1)	27 (7.5)	15 (4.7)	11 (3.6)	36 (10.0)	35 (9.7)
Nonprotein Nitrogen Increased	4 (1.1)	3 (0.8)	10 (3.2)	15 (4.9)	14 (3.9)	17 (4.7)
Hyperglycemia	10 (2.8)	8 (2.2)	4 (1.3)	2 (0.7)	13 (3.6)	9 (2.5)
LDH Increased	5 (1.4)	7 (1.9)	0 (0.0)	2 (0.7)	5 (1.4)	9 (2.5)
Hyperphosphatemia	2 (0.6)	1 (0.3)	3 (0.9)	5 (1.6)	5 (1.4)	6 (1.7)
HEMATOLOGIC						
Anemia	41 (11.4)	41 (11.4)	5 (1.6)	10 (3.3)	44 (12.2)	51 (14.1)
Lymphopenia	38 (10.5)	37 (10.2)	10 (3.2)	9 (3.0)	46 (12.7)	45 (12.5)
Neutropenia	22 (6.1)	21 (5.8)	27 (8.5)	24 (7.9)	45 (12.5)	41 (11.4)
Leukopenia	16 (4.4)	11 (3.0)	11 (3.5)	9 (3.0)	24 (6.6)	17 (4.7)
Leukocytosis	6 (1.7)	13 (3.6)	5 (1.6)	2 (0.7)	11 (3.0)	15 (4.2)
Neutrophilia	5 (1.4)	11 (3.0)	4 (1.3)	2 (0.7)	9 (2.5)	13 (3.6)
Thrombocytosis	20 (5.5)	13 (3.6)	1 (0.3)	0 (0.0)	20 (5.5)	13 (3.6)
Thrombocytopenia	6 (1.7)	6 (1.7)	4 (1.3)	6 (2.0)	9 (2.5)	11 (3.0)
Polycythemia	3 (0.8)	2 (0.6)	5 (1.6)	3 (1.0)	8 (2.2)	5 (1.4)
Lymphadenopathy	4 (1.1)	2 (0.6)	0 (0.0)	2 (0.7)	4 (1.1)	4 (1.1)
BODY AS A WHOLE - GENERAL						
Back Pain	15 (4.2)	11 (3.0)	11 (3.5)	4 (1.3)	25 (6.9)	15 (4.2)
Pain	14 (3.9)	17 (4.7)	8 (2.5)	5 (1.6)	22 (6.1)	22 (6.1)
Chest Pain	10 (2.8)	11 (3.0)	10 (3.2)	5 (1.6)	20 (5.5)	16 (4.4)
Injury Accident	5 (1.4)	5 (1.4)	12 (3.8)	14 (4.6)	17 (4.7)	17 (4.7)
Abdominal Pain	3 (0.8)	3 (0.8)	4 (1.3)	4 (1.3)	7 (1.9)	7 (1.9)
Fever	5 (1.4)	7 (1.9)	1 (0.3)	1 (0.3)	5 (1.4)	7 (1.9)

Fatigue	3 (0.8)	1 (0.3)	1 (0.3)	3 (1.0)	4 (1.1)	4 (1.1)
Edema Dependent	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
DERMATOLOGIC						
Rash	15 (4.2)	26 (7.2)	8 (2.5)	8 (2.6)	22 (6.1)	33 (9.1)
Sweating Increased	19 (5.3)	18 (5.0)	5 (1.6)	4 (1.3)	23 (6.4)	22 (6.1)
Pruritus	10 (2.8)	16 (4.4)	3 (0.9)	0 (0.0)	13 (3.6)	16 (4.4)
Acne	9 (2.5)	5 (1.4)	0 (0.0)	3 (1.0)	9 (2.5)	8 (2.2)
Skin Disorder	2 (0.6)	3 (0.8)	3 (0.9)	5 (1.6)	5 (1.4)	8 (2.2)
Rash Maculopapular	6 (1.7)	3 (0.8)	0 (0.0)	1 (0.3)	6 (1.7)	4 (1.1)
Eczema	2 (0.6)	2 (0.6)	3 (0.9)	2 (0.7)	4 (1.1)	3 (0.8)
RESPIRATORY						
Hemoptysis	27 (7.5)	20 (5.5)	6 (1.9)	6 (2.0)	30 (8.3)	25 (6.9)
Coughing	21 (5.8)	8 (2.2)	9 (2.8)	11 (3.6)	29 (8.0)	17 (4.7)
Upper Respiratory Tract Infection	5 (1.4)	9 (2.5)	12 (3.8)	15 (4.9)	17 (4.7)	22 (6.1)
Bronchitis	1 (0.3)	1 (0.3)	8 (2.5)	1 (0.3)	9 (2.5)	2 (0.6)
Pharyngitis	5 (1.4)	0 (0.0)	2 (0.6)	5 (1.6)	7 (1.9)	5 (1.4)
Epistaxis	2 (0.6)	2 (0.6)	3 (0.9)	1 (0.3)	5 (1.4)	3 (0.8)
Pleuritis	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
GASTROINTESTINAL						
Dyspepsia	6 (1.7)	11 (3.0)	4 (1.3)	6 (2.0)	10 (2.8)	17 (4.7)
Vomiting	6 (1.7)	14 (3.9)	3 (0.9)	3 (1.0)	9 (2.5)	17 (4.7)
Nausea	7 (1.9)	3 (0.8)	2 (0.6)	1 (0.3)	9 (2.5)	4 (1.1)
Constipation	6 (1.7)	1 (0.3)	2 (0.6)	1 (0.3)	7 (1.9)	2 (0.6)
Diarrhea	5 (1.4)	2 (0.6)	2 (0.6)	0 (0.0)	7 (1.9)	2 (0.6)
Hemorrhoids	4 (1.1)	0 (0.0)	1 (0.3)	0 (0.0)	5 (1.4)	0 (0.0)
INFECTIOUS DISEASE						
Influenza	9 (2.5)	8 (2.2)	22 (6.9)	12 (3.9)	28 (7.8)	20 (5.5)
Infection Tuberculosis	0 (0.0)	5 (1.4)	9 (2.8)	4 (1.3)	9 (2.5)	9 (2.5)
Infection	1 (0.3)	2 (0.6)	4 (1.3)	4 (1.3)	5 (1.4)	6 (1.7)
Herpes Zoster	2 (0.6)	0 (0.0)	2 (0.6)	3 (1.0)	4 (1.1)	3 (0.8)
HEPATIC & BILIARY						
ALT Increased	18 (5.0)	23 (6.4)	7 (2.2)	10 (3.3)	25 (6.9)	32 (8.9)
AST Increased	15 (4.2)	18 (5.0)	7 (2.2)	8 (2.6)	21 (5.8)	26 (7.2)
NEUROLOGIC						
Headache	11 (3.0)	13 (3.6)	3 (0.9)	7 (2.3)	14 (3.9)	20 (5.5)
Dizziness	5 (1.4)	5 (1.4)	1 (0.3)	1 (0.3)	6 (1.7)	6 (1.7)
Tremor	3 (0.8)	1 (0.3)	2 (0.6)	0 (0.0)	5 (1.4)	1 (0.3)
PSYCHIATRIC						
Anorexia	14 (3.9)	18 (5.0)	8 (2.5)	6 (2.0)	21 (5.8)	22 (6.1)
Insomnia	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.7)	4 (1.1)	4 (1.1)
MUSCULOSKELETAL						

Arthralgia	13 (3.6)	13 (3.6)	3 (0.9)	5 (1.6)	16 (4.4)	18 (5.0)
Arthritis	4 (1.1)	5 (1.4)	1 (0.3)	0 (0.0)	4 (1.1)	5 (1.4)
Arthrosis	4 (1.1)	1 (0.3)	0 (0.0)	1 (0.3)	4 (1.1)	2 (0.6)
Gout	3 (0.8)	1 (0.3)	1 (0.3)	0 (0.0)	4 (1.1)	1 (0.3)
CARDIOVASCULAR						
Hypertension	3 (0.8)	5 (1.4)	3 (0.9)	2 (0.7)	6 (1.7)	7 (1.9)
OPHTHALMOLOGIC						
Conjuctivitis	8 (2.2)	2 (0.6)	1 (0.3)	1 (0.3)	9 (2.5)	3 (0.8)
Note: ≥1% refers to rifapentine in the TOTAL column.						

*****Initial Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid, pyrazinamide, and ethambutol administered daily (rifapentine twice weekly) for 60 days.
†Continuation Phase consisted of therapy with either rifapentine or rifampin combined with isoniazid for 120 days. Rifapentine patients were dosed once weekly; rifampin patients were dosed twice weekly.
‡A patient may have experienced the same adverse reaction more than once during the course of the study, therefore, patient counts across the columns may not equal the patient counts in the TOTAL column.

In addition to the adverse reactions reported in Table 1, adverse reactions were reported post-treatment during the 3 month through 24 month follow-up period. Although the protocol for this study specified collection of serious adverse reactions during this period, some non-serious adverse reactions were reported as well. For the rifapentine combination group these included the following: hematuria, infection tuberculosis, proteinuria, urinary casts, hyperkalemia, hypoglycemia, injury accident, skin disorder, respiratory disorder, stupor, prostatic disorder.
Treatment-emergent adverse reactions reported during treatment and post-treatment through the first three months of follow-up in <1% of the rifapentine combination therapy patients are presented below by body system in order of frequency.
Renal & Urinary: urethral disorder, dysuria, pyelonephritis, urinary incontinence, urination disorder.
Metabolic & Nutritional: weight decrease, BUN increased, diabetes mellitus, alkaline phosphatase increased, hypophosphatemia, hypercalcemia, hypovolemia, weight increase.
Hematologic: lymphocytosis, hematoma, purpura, anemia hypochromic, anemia normocytic, thrombosis.
Body as a Whole - General: laboratory test abnormal, edema legs, asthenia, edema face, abscess, edema peripheral, malaise.
Dermatologic: skin ulceraction, urticaria, dry skin, furunculosis, skin discoloration, dermatitis fungal, nail disorder, alopecia, rash erythematous.
Respiratory: abnormal breath sounds, pneumothorax, pneumonia, pleural effusion, rhinitis, dyspnea, pneumonitis, sinusitis, sputum increased, pulmonary fibrosis, upper respiratory congestion, asthma, chest x-ray abnormal, bronchospasm, laryngeal edema, laryngitis, respiratory disorder,
Gastrointestinal: tooth disorder, gastroenteritis, gastritis, esophagitis, cheilitis, dry mouth, pancreatitis, proctitis, salivary gland enlargement, tenesmus, gastrointestinal disorder not specified.
Infectious Disease: infection fungal, infection parasitic, infection protozoan.
Hepatic & Biliary: bilirubinemia, hepatomegaly, jaundice.
Neurologic: somnolence, seizure not specified, dysphonia, hypoesthesia, torticollis, hypertonia, hyporeflexia, meningitis, migraine headache, stupor.
Psychiatric: anxiety, confusion, drug abuse, aggressive reaction, agitation.
Musculoskeletal: myalgia, myositis, bone fracture, muscle weakness, muscle spasm.
Cardiovascular: syncope, tachycardia, palpitation, hypotension orthostatic, pericarditis.
Reproductive Disorders: penis disorder, vaginitis, vaginal hemorrhage, cervical smear test positive, leukorrhea, mastitis male, prostatic disorder.
Hearing & Vestibular: ear disorder not specified, otitis media, earache, otitis externa, tympanic membrane perforation.
Ophthalmologic: eye pain, eye abnormality.
Neoplasms: pulmonary carcinoma, neoplasm not specified, carcinoma, lipoma.
Vascular (Extracardiac): thrombophlebitis deep, vascular disorder, vasodilation.
Special Senses Other: taste loss.
Pregnancy, puerperium and perinatal conditions: abortion
In another randomized, open-label trial in 1075 HIV seronegative and seropositive patients with pulmonary tuberculosis the overall adverse event rate did not differ substantially from the previous trial. Patients who had completed an initial 2 month phase of treatment with 4 drugs were randomly assigned to receive either rifapentine 600 mg and isoniazid once weekly or rifampin and isoniazid twice weekly for the 4 month continuation phase.

In the rifapentine arm, 502 HIV seronegative and 36 HIV seropositive patients were randomized and in the rifampin arm 502 HIV seronegative and 35 HIV seropositive patients were randomized to treatment.
The death rate among all study participants was 71/1075 (6.6%) and did not differ between the two treatment groups (6.5% for the rifapentine combination regimen compared to 6.7% for the rifampin combination regimen; $P = 0.87$).
There were 526 treatment-emergent adverse events regardless of causality reported from 251 patients treated with the rifapentine combination regimen and 513 adverse events reported from 248 patients treated with the rifampin combination regimen. On both study arms the most frequently reported adverse events were hyperglycemia, pneumonia, liver toxicity, and death and were consistent with concurrent underlying conditions that included alcohol abuse, pancreatitis and HIV.
There was a greater percentage of patients in the rifampin combination arm who developed hepatic adverse events (35/513; 6.8 %) compared to 20/526 (3.8%) in the rifapentine combination arm. The types of other adverse events were similar between the treatment arms.
Hyperuricemia was not reported as an adverse reaction in this study of continuation phase therapy. In the previous study which evaluated initial therapy containing pyrazinamide, hyperuricemia was reported in 32% of rifapentine and 23% of rifampin combination treated patients (see Table 1).

7 DRUG INTERACTIONS

7.1 Protease Inhibitors and Reverse Transcriptase Inhibitors
Rifapentine is an inducer of CYP450 enzymes. Concomitant use of PRIFTIN with other drugs metabolized by these enzymes, such as protease inhibitors and reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor. *[see Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)]*

7.2 Hormonal Contraceptives
PRIFTIN may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

7.3 Cytochrome P450 3A4 and 2C8/9
Rifapentine is an inducer of cytochromes P4503A4 and P4502C8/9. Therefore, rifapentine may increase the metabolism of other coadministered drugs that are metabolized by these enzymes. Induction of enzyme activities by rifapentine occurred within 4 days after the first dose. Enzyme activities returned to baseline levels 14 days after discontinuing rifapentine. In addition, the magnitude of enzyme induction by rifapentine was dose and dosing frequency dependent; less enzyme induction occurred when 600 mg oral doses of rifapentine were given once every 72 hours versus daily.
In vitro and in vivo enzyme induction studies have suggested rifapentine induction potential may be less than rifampin but more potent than rifabutin.
Rifampin has been reported to accelerate the metabolism and may reduce the activity of the following drugs; hence, rifapentine may also increase the metabolism and decrease the activity of these drugs. Dosage adjustments of the drugs in Table 2 or of other drugs metabolized by cytochrome P4503A4 or P4502C8/9 may be necessary if they are given concurrently with rifapentine.
Table 2. Drug Interactions with PRIFTIN: Dosage Adjustment may be Necessary

Drug Class	Examples of Drugs Within Class
Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide
Antibiotics	Chloramphenicol, clarithromycin, dapsone, doxycycline; Fluoroquinolones (such as ciprofloxacin)
Oral Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Azole Antifungals	Fluconazole, itraconazole, ketoconazole
Antipsychotics	Haloperidol
Barbiturates	Phenobarbital
Benzodiazepines	Diazepam
Beta-Blockers	Propanolol
Calcium Channel Blockers	Diltiazem, nifedipine, verapamil
Cardiac Glycoside Preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Oral Hypoglycemics	Sulfonylureas (e.g., glyburide, glipizide)

Hormonal Contraceptives/ Progestins	Ethinyl estradiol, levonorgestrel
Immunosuppressants	Cyclosporine, tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Phophodiesterase-5 (PDE-5) Inhibitors	Sildenafil
Thyroid preparations	Levothyroxine
Tricyclic antidepressants	Amitriptyline, nortriptyline

7.4 Other Interactions
The conversion of rifapentine to 25-desacetyl rifapentine is mediated by an esterase enzyme. There is minimal potential for rifapentine metabolism to be inhibited or induced by another drug, or for rifapentine to inhibit the metabolism of another drug based upon the characteristics of the esterase enzymes.
Rifapentine does not induce its own metabolism *[see Clinical Pharmacology (12.3)]*.
Since rifapentine is highly bound to albumin, drug displacement interactions may also occur *[see Clinical Pharmacology (12.3)]*.

7.5 Interactions with Laboratory Tests
Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B_{12}. Similar drug-laboratory interactions should be considered for rifapentine; thus, alternative assay methods should be considered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C: There are no adequate and well controlled studies of rifapentine use during pregnancy. In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic. However, because animal studies are not always predictive of human response, rifapentine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When administered during the last few weeks of pregnancy, rifampin, another rifamycin, may increase the risk for maternal postpartum hemorrhage and bleeding in the exposed infant. Therefore, pregnant women and their infants, who are exposed to rifapentine during the last few weeks of pregnancy, should have appropriate monitoring of clotting parameters. Treatment with Vitamin K may be indicated.

Six patients randomized to rifapentine became pregnant during a study of initial treatment of tuberculosis. Two delivered normal infants; two had first trimester spontaneous abortions; one had an elective abortion; and one patient was lost to follow-up. The two patients who spontaneously aborted had co-morbid conditions: One patient abused ethanol and the other patient was HIV positive.

Animal studies in rats and rabbits revealed embryofetal toxicity in both species. Pregnant rats given rifapentine during organogenesis at doses 0.6 times the human dose (based on body surface area), produced pups with cleft palates, right aortic arch, increased incidence of delayed ossification, and increased numbers of ribs. When rifapentine was administered to mated female rats late in gestation, at 0.3 times the human dose (based on body surface area), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls. Increased resorptions and post implantation loss, decreased mean fetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received rifapentine at doses 0.3 to 1.3 times the human dose (based on body surface area), major fetal malformations occurred including: ovarian agenesis, pes varus, arhinia, microphthalmia and irregularities of the ossified facial tissues. At the higher dose, there were increases in post-implantation loss and the incidence of stillborn pups.

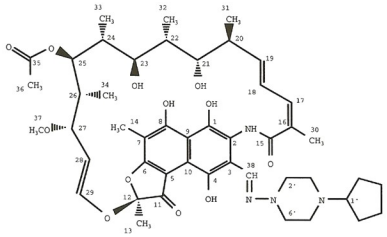
8.3 Nursing Mothers
It is not known whether rifapentine is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother and the benefits of breastfeeding. Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.
A slight increase in rat pup mortality was observed during lactation when dams were dosed late in gestation through lactation.

8.4 Pediatric Use
The safety and effectiveness of rifapentine in pediatric patients under the age of 12 have not been established. A pharmacokinetic study was conducted in 12- to 15-year-old healthy volunteers and the pharmacokinetics of rifapentine were similar to those observed in healthy adults *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use
The Clinical studies of PRIFTIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
There is no experience with the treatment of acute overdose with rifapentine at doses exceeding 1200 mg per dose.
In a pharmacokinetic study involving healthy volunteers (n=9), single oral doses up to 1200 mg have been administered without serious adverse events. The only adverse events reported with the 1200 mg dose were heartburn (3/8), headache (2/8) and increased urinary frequency (1/8). In clinical trials, tuberculosis patients ranging in age from 20 to 74 years accidentally received continuous daily doses of rifapentine 600 mg. Some patients received continuous daily dosing for up to 20 days without evidence of serious adverse effects. One patient experienced a transient elevation in SGPT and glucose (the latter attributed to pre-existing diabetes); a second patient experienced slight pruritus. While there is no experience with the treatment of acute overdose with rifapentine, clinical experience with rifamycins suggests that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by instillation of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract. Rifapentine and 25-desacetyl rifapentine are 97.7% and 93.2% plasma protein bound, respectively. Rifapentine and related compounds excreted in urine account for only 17% of the administered dose, therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifapentine from the body of a patient with PRIFTIN overdose.

11 DESCRIPTION
PRIFTIN (rifapentine) for oral administration contains 150 mg of the active ingredient rifapentine per tablet.
The 150 mg tablets also contain, as inactive ingredients: calcium stearate, disodium EDTA, FD&C Blue No. 2 aluminum lake, hydroxypropyl cellulose, hypromellose USP, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate, synthetic red iron oxide, and titanium dioxide.
Rifapentine is a rifamycin derivative antibiotic and has a similar profile of microbiological activity to rifampin (rifampicin). The molecular weight is 877.04.
The molecular formula is $C_{47}H_{64}N_4O_{12}$.
The chemical name for rifapentine is rifamycin, 3-[[(4-cyclopentyl-1-piperazinyl)imino]methyl]- or 3-[N-(4-Cyclopentyl-1-piperazinyl)formimidoyl] rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-l-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate. It has the following structure:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Rifapentine, a cyclopentyl rifamycin, is an antimycobacterial agent [see *Clinical Pharmacology, Microbiology (12.4)*].

12.3 Pharmacokinetics
Absorption

The absolute bioavailability of rifapentine has not been determined. The relative bioavailability (with an oral solution as a reference) of rifapentine after a single 600 mg dose to healthy adult volunteers was 70%. The maximum concentrations were achieved from 5 to 6 hours after administration of the 600 mg rifapentine dose.

The administration of rifapentine with a high fat meal (850 total calories: 33 g protein, 55 g fat and 58 g carbohydrate) increased AUC(0–∞) and C_{max} by 43% and 44%, respectively over that observed when administered under fasting conditions.

When oral doses of rifapentine were administered once daily or once every 72 hours to healthy volunteers for 10 days, single dose AUC(0–∞) value of rifapentine was similar to its steady-state AUC_{ss} (0–24h) or AUC_{ss} (0–72h) values, suggesting no significant auto-induction effect on steady-state pharmacokinetics of rifapentine. Steady-state conditions were achieved by day 10 following daily administration of rifapentine 600 mg.

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine (active metabolite) on day 10 following oral administration of 600 mg rifapentine every 72 hours to healthy volunteers are contained in Table 3.

Table 3. Pharmacokinetics and rifapentine and 25-desacetyl rifapentine in healthy volunteers.

Parameter	**Rifapentine**	**25-desacetyl Rifapentine**
	Mean ± SD (n=12)	
C_{max} (µg/mL)	15.05 ± 4.62	6.26 ± 2.06
AUC (0–72h)(µg*h/mL)	319.54 ± 91.52	215.88 ± 85.96
$T_{1/2}$(h)	13.19 ± 1.38	13.35 ± 2.67
T_{max} (h)	4.83 ± 1.80	11.25 ± 2.73
Clpo (L/h)	2.03 ± 0.60	--

Distribution

In a population pharmacokinetic analysis in 351 tuberculosis patients who received 600 mg rifapentine in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent volume of distribution was 70.2 ± 9.1 L. In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 97.7% and 93.2% bound to plasma proteins, respectively. Rifapentine was mainly bound to albumin. Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and hepatically impaired subjects.

Metabolism/Excretion

Following a single 600 mg oral dose of radiolabeled rifapentine to healthy volunteers (n=4), 87% of the total ^{14}C rifapentine was recovered in the urine (17%) and feces (70%). Greater than 80% of the total ^{14}C rifapentine dose was excreted from the body within 7 days. Rifapentine was hydrolyzed by an esterase enzyme to form a microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma. Plasma AUC(0–∞) and C_{max} values of the 25-desacetyl rifapentine metabolite were one-half and one-third those of the rifapentine, respectively. Based upon relative in vitro activities and AUC(0–∞) values, rifapentine and 25-desacetyl rifapentine potentially contributes 62% and 38% to the clinical activities against *M. tuberculosis*, respectively.

Special Populations

Gender: In a population pharmacokinetics analysis of sparse blood samples obtained from 351 tuberculosis patients who received 600 mg rifapentine in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent oral clearance of rifapentine for males and females was 2.51 ± 0.14 L/h and 1.69 ± 0.41 L/h, respectively. The clinical significance of the difference in the estimated apparent oral clearance is not known.

Elderly: Following oral administration of a single 600 mg dose of rifapentine to elderly (≥65 years) male healthy volunteers (n=14), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar to that observed for young (18 to 45 years) healthy male volunteers (n=20).

Pediatric (Adolescents): In a pharmacokinetics study of rifapentine in healthy adolescents (age 12 to 15), 600 mg rifapentine was administered to those weighing ≥45 kg (n=10) and 450 mg was administered to those weighing <45 kg (n=2). The pharmacokinetics of rifapentine were similar to those observed in healthy adults.

Renal Impaired Patients: The pharmacokinetics of rifapentine have not been evaluated in renal impaired patients. Although only about 17% of an administered dose is excreted via the kidneys, the clinical significance of impaired renal function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Hepatic Impaired Patients: Following oral administration of a single 600 mg dose of rifapentine to mild to severe hepatic impaired patients (n=15), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment and to that observed in another study for healthy volunteers (n=12). Since the elimination of these agents are primarily via the liver, the clinical significance of impaired hepatic function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Asymptomatic HIV-Infected Volunteers: Following oral administration of a single 600 mg dose of rifapentine to asymptomatic HIV-infected volunteers (n=15) under fasting conditions, mean C_{max} and AUC(0–∞) of rifapentine were lower (20–32%) than that observed in other studies in healthy volunteers (n=55). In a cross-study comparison, mean C_{max} and AUC values of the 25-desacetyl

metabolite of rifapentine, when compared to healthy volunteers were higher (6–21%) in one study (n=20), but lower (15–16%) in a different study (n=40). The clinical significance of this observation is not known. Food (850 total calories: 33 g protein, 55 g fat, and 58 g carbohydrate) increases the mean AUC and C_{max} of rifapentine observed under fasting conditions in asymptomatic HIV-infected volunteers by about 51% and 53%, respectively.

Drug-Drug Interactions: Rifapentine is an inducer of cytochrome P4503A4 and 2C8/9. Therefore, it may increase the metabolism and decrease the activity of other co-administered drugs that are metabolized by these enzymes. Dosage adjustments of the co-administered drugs may be necessary if they are given concurrently with rifapentine *[see Drug Interactions (7.3)]*.

Indinavir: In a study in which 600 mg rifapentine was administered twice weekly for 14 days followed by rifapentine twice weekly plus 800 mg indinavir 3 times a day for an additional 14 days, indinavir C_{max} decreased by 55% while AUC reduced by 70%. Clearance of indinavir increased by 3-fold in the presence of rifapentine while half-life did not change. But when indinavir was administered for 14 days followed by coadministration with rifapentine for an additional 14 days, indinavir did not affect the pharmacokinetics of rifapentine *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)]*.

12.4 Microbiology
Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* but not in mammalian cells. At therapeutic levels, rifapentine exhibits bactericidal activity against both intracellular and extracellular *M. tuberculosis* organisms. Both rifapentine and the 25-desacetyl metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of approximately 24:1 and 7:1, respectively.

In Vitro Activity

Rifapentine and its 25-desacetyl metabolite have demonstrated *in vitro* activity against rifamycin-susceptible strains of *Mycobacterium tuberculosis* including cidal activity against phagocytized *M. tuberculosis* organisms grown in activated human macrophages.

The correlation between rifapentine MICs and clinical cure has not been established. Interpretive criteria/breakpoints to determine whether clinical isolates of *M. tuberculosis* are susceptible or resistant to rifapentine have not been established.

In Vivo Activity

In mouse infection studies a therapeutic effect, in terms of enhanced survival time or reduction of organ bioburden, has been observed in *M. tuberculosis*-infected animals treated with various intermittent rifapentine containing regimens. Animal studies have shown that the activity of rifapentine is influenced by dose and frequency of administration.

Drug Resistance

In the treatment of tuberculosis, a small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. Rifapentine resistance development in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in the *rpo*B portion of the gene coding for the beta subunit of the DNA-dependent RNA polymerase. The incidence of rifapentine resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10^7 to 10^8 bacilli.

Cross Resistance

M. tuberculosis organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampin and rifapentine has been demonstrated with *M. tuberculosis* strains. Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Fertility, Carcinogenesis, Mutagenesis

Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winklemann) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 th of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions).

Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test); in vitro point mutation test in *Aspergillus nidulans*; in vitro gene conversion assay in *Saccharomyces cerevisiae*; host-mediated (mouse) gene conversion assay with *Saccharomyces cerevisiae*; in vitro Chinese hamster ovary cell/hypoxanthineguanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

The 25-desacetyl metabolite of rifapentine was positive in the *in vitro* mammalian chromosome aberration test in V79 Chinese Hamster cells, but was negative in the in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/ hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to one-third of the human dose (based on body surface area conversions).

14 CLINICAL STUDIES

Rifapentine was studied in two randomized, open-label controlled clinical trials.

The first trial was an open-label, prospective, parallel group, active controlled trial in patients with pulmonary tuberculosis, excluding those with HIV-infection. The population was mostly comprised of Black (> 60%) or Multiracial (>31%) patients. Treatment groups were comparable for age and sex and consisted primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2 month phase of treatment (60 days), 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin 600 mg in combination with isoniazid, pyrazinamide and ethambutol all administered daily. The doses of the companion drugs were the same in both treatment arms during the initial phase: isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1200 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg), pyrazinamide (1500 mg) and ethambutol (800 mg) were reduced. Ethambutol was discontinued when isoniazid and rifampin susceptibility testing results were confirmed. During the 4 month continuation phase, 321 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid 300 mg and 307 patients in the rifampin arm received twice weekly rifampin and isoniazid 900 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg) and isoniazid (600 mg) were reduced. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period. Treatment was directly observed. Despite observed therapy, 65/361 (18%) of patients in the rifapentine arm and 34/361 (9%) in the rifampin arm received overdoses of one or more of the administered study medications during the initial or continuation phase of treatment. Only seven of these patients had adverse reactions reported with the overdose (5 in the rifapentine group and 2 in the rifampin group).

Table 4 below contains assessments of sputum conversion at end of treatment (6 months) and relapse rates at the end of follow-up (24 months).

Table 4. Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

	Rifapentine Combination Treatment % and (n/N*)	**Rifampin Combination Treatment % and (n/N*)**
Status at End of 6 months of Treatment		
Converted	87% (248/286)	80% (226/283)
Not Converted	1% (4/286)	3% (8/283)
Lost to Follow-up	12% (34/286)	17% (49/283)
Status Through 24 Month Follow-up†:		
Relapsed	12% (29/248)	7% (15/226)
Sputum Negative	57% (142/248)	64% (145/226)
Lost to Follow-up	31% (77/248)	29% (66/226)

*****All data for patients with confirmed susceptible *M. tuberculosis* (rifapentine combination treatment, N=286; rifampin combination treatment, N=283).

†Twenty-two (22) deaths occurred during the study; 11 in each treatment arm

Risk of relapse was greater in the group treated with the rifapentine combination. Higher relapse rates were associated with a lower rate of compliance with the companion antituberculosis drugs as well as a failure to convert sputum cultures at the end of the initial 2 month treatment phase. Relapse rates were also higher for males in both regimens. Relapse in the rifapentine group was not associated with development of mono-resistance to rifampin.

In vitro susceptibility testing was conducted against *M. tuberculosis* isolates recovered from 620 patients enrolled in the study. Rifapentine and rifampin MIC values were determined employing the radiometric susceptibility testing method utilizing 7H12 broth at pH 6.8 (CLSI procedure M24-A; (1)). Six hundred and twelve patients had *M. tuberculosis* isolates that were susceptible to rifampin (MIC < 0.5 µg/ml). Of these patients, six hundred and ten had *M. tuberculosis* isolates (99.7%) with rifapentine MICs of < 0.125 µg/ml. The other two patients that had rifampin susceptible *M. tuberculosis* isolates had rifapentine MICs of 0.25 µg/ml. The remaining eight patients had *M. tuberculosis* isolates that were resistant to rifampin (MIC > 8.0 µg/ml). These *M. tuberculosis* isolates had rifapentine MICs of > 8.0 µg/ml. In this study high rifampin and rifapentine MICs were associated with multi-drug resistant *M.*

tuberculosis (MDRTB) isolates. Rifampin monoresistance was not observed in either treatment arm. This information is provided for comparative purposes only as rifapentine breakpoints have not been established.
The second trial was a randomized, open-label trial in 1075 HIV seronegative and seropositive patients with pulmonary tuberculosis. Patients with culture-positive, drug-susceptible pulmonary tuberculosis who had completed the initial 2 month phase of treatment with 4 drugs (rifampin, isoniazid, pyrazinamide, and either ethambutol or streptomycin) under direct observation were randomly assigned to receive either rifapentine 600 mg and isoniazid 15 mg/kg (max 900 mg) once weekly or rifampin 10 mg/kg (max 600 mg) and isoniazid 15 mg/kg (max 900 mg) twice weekly for the 4 month continuation phase. Study drugs were given under direct observation therapy in both arms.
In the rifapentine arm, 502 HIV seronegative and 36 HIV seropositive patients were randomized and in the rifampin arm 502 HIV seronegative and 35 HIV seropositive patients were randomized to treatment. Enrollment of HIV seropositive patients was stopped when 4 of 36 patients in the rifapentine combination group developed rifampin monoresistance.
Table 5 below contains assessments of sputum conversion at the end of treatment (6 months total: 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV seronegative patients randomized to treatment. The failure and relapse rates reported in this study could be underestimated due to the limitation of the microbiologic methods used in the study. Positive culture was based on either one sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.
Table 5: Clinical Outcome in HIV Negative Patients with Pulmonary Tuberculosis

	Rifapentine Combination Treatment % (n/N)	**Rifampin Combination Treatment % (n/N)**
Status at End of 4 Months Continuation Phase		
Treatment Response *	93.8% (471/502)	91.0% (457/502)
Not Converted	1.0% (5/502)	1.2% (6/502)
Did Not Complete Treatment†	4.2% (21/502)	7.0% (35/502)
Deaths	1.0 % (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)
Deaths	4.0% (19/471)	5.3% (24/457)

*****Treatment response was defined as subjects who responded successfully after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, and remained sputum negative through the end of continuation phase therapy.
†Due to drug toxic effects, non-adherence, withdrawal of consent, receipt of nonstudy regimen, other.

Higher relapse rates in HIV seronegative patients were seen in patients with a positive sputum culture at 2 months (i.e., at the time of study randomization), cavitation on chest x-ray, and bilateral pulmonary involvement.
Seventy-one HIV seropositive patients were enrolled into the study. There were no treatment failures during the study phase therapy. Sixty-one patients completed therapy and were assessed for relapse. The rates of relapse were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group.
Risk factors that predisposed to relapse in the HIV seropositive patients included the presence of both pulmonary and extrapulmonary disease at baseline, low CD4 counts, use of azole antifungals and younger age.
In HIV seropositive patients, 4 of the 5 relapses from the rifapentine combination group involved *M. tuberculosis* strains with rifampin monoresistance (RMR). No relapse strain in the twice weekly rifampin/isoniazid group had acquired drug resistance. These data are consistent with other documented acquired rifampin monoresistance in HIV seropositive adults who fail or relapse after treatment with intermittent regimens with isoniazid and other rifamycins (rifampin and rifabutin).
The death rate among all study participants did not differ between the two treatment groups.

15 REFERENCES

1. Clinical and Laboratory Standards Institute. M24-A Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard. 23 ed. 2003. Clinical Laboratory Standards Institute, Wayne, PA

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PRIFTIN is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed "Priftin" on top and "150" on the bottom, packaged in aluminum formable foil blister strips placed in cartons of 32 tablets (4 strips of 8). Each strip of 8 tablets is inserted into an aluminum foil laminated pouch. (NDC 0088-2100-03).

Storage

Store at 25°C (77°F); excursions permitted 15–30°C (59–86°F) (see USP Controlled Room Temperature). Protect from excessive heat and humidity.

17 PATIENT COUNSELING INFORMATION

17.1 Compliance

Compliance with the full course of therapy must be emphasized to the patient, and the importance of not missing any doses of the daily administered companion medications in the Initial Phase must be stressed.

17.2 Drug Interactions

Rifapentine may increase the metabolism and decrease the activity of other drugs that are metabolized by the P4503A4 and 2C8/9 pathways. Dosage adjustments of the co-administered drugs may be necessary. Patients should be advised to discuss with their physician the other medications they are taking before starting treatment with rifapentine.

Concomitant use of rifapentine with protease inhibitors or reverse transcriptase inhibitors may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor.

Rifapentine may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

17.3 Discoloration of Body Fluids

The patient should be informed that PRIFTIN may produce a reddish coloration of the urine, sweat, sputum, tears, and breast milk and the patient should be forewarned that contact lenses or dentures may be permanently stained.

17.4 Adverse Reactions

Patients should be instructed to notify their physician promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, and pain or swelling of the joints.

17.5 Administration with Food

For those patients with a propensity to experience nausea, vomiting, or gastrointestinal upset, inform those patients that administration of PRIFTIN with food may be useful.

Revised June 2009

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

PRINCIPAL DISPLAY PANEL - 150 MG BLISTER

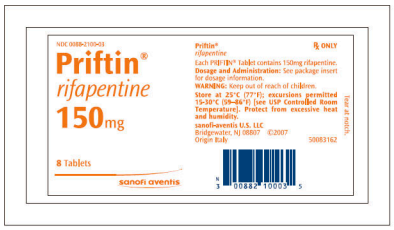
NDC 0088-2100-03

Priftin® 150mg
rifapentine
sanofi-aventis U.S. LLC Origin Italy
Peel at unsealed corners
50083161 89018142

PRINCIPAL DISPLAY PANEL - 150 MG POUCH

NDC 0088-2100-03

Priftin®
rifapentine
150mg
8 Tablets
sanofi-aventis



PRINCIPAL DISPLAY PANEL - 150 MG CARTON

NDC 0088-2100-03

Priftin®

rifapentine

150mg

32 Tablets

Four 8-Tablet Pouches

sanofi-aventis